IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Applicants: Robert Tridgett *et al.*
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Examiner: Craig D. Ricci

DECLARATION OF PHILIP PAUL NICHOLS

I, Philip Paul Nichols, of Hauxley Hall, Hauxley, Morpeth, Northumberland NE65 0JP Great Britain, do hereby declare and state as follows:

1. I am currently Senior Lecturer at the University of Newcastle, United Kingdom and Honorary Consultant Neurologist at the Royal Victoria Infirmary in Newcastle, United Kingdom, both of which posts I have held since 2002. From 2006 to 2009, I was also Chief Medical Officer (CMO) & Head of Clinical Development at Cambridge Laboratories Limited, an associate company of Cambridge Laboratories (Ireland) Limited, the applicant for the International patent application PCT/GB2005/000464 from which the present application serial number 10/597,803 ("the '803 application") is derived.

2. I hold a medical degree (MBBS) and the degree of BMedSci, both from the University of Newcastle, and a doctorate (DPhil) in medicine from the University of Oxford, United Kingdom. I am also a Member of the Royal College of Physicians.

3. During my time as CMO at Cambridge Laboratories Limited, I had primary responsibility for the clinical development of *cis*-dihydrotetrabenazines described in the '803 application.

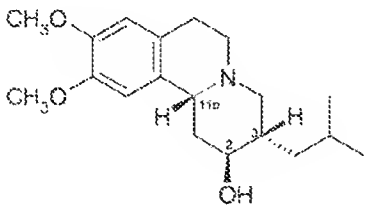
4. A number of studies have been carried out by or on behalf of Cambridge Laboratories in which the potential sedating properties of the compounds of '803 application have been investigated. These studies are discussed below.

5. MDS Study AA23604

   This study examined the effect of three test compounds, tetrabenazine (TBZ), RUS 345 (Isomer C in the '803 application) and RUS 350 (Isomer B in the '803 application) on

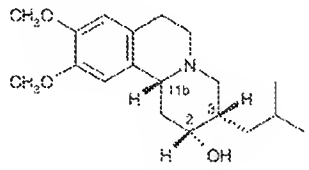
spontaneous locomotor activity in male rats as a measure of the relative sedative properties of the three compounds.

Isomer B has the structure:



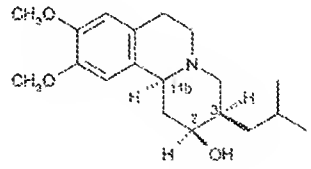
(Isomer B)

Isomer C has one of the following two structures:



2*R*,3*S*,11b*R*

OR



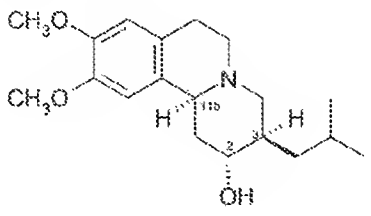
2*S*,3*R*,11b*S*

Doses of 0.3, 1, 3 & 10 mg/kg were given by intra-peritoneal injection. Locomotor activity was measured 45 minutes and 3 hours post dosing. The study concluded that TBZ induced sedation at 45 minutes and 3 hours after administration to rats. This effect was dose dependent and statistically significant at 3 and 10 mg/kg i.p. RUS 345 (Isomer C) and RUS 350 (Isomer B) had no sedative effect at any of the doses tested.

6. KWS Biotest Studies CAM003-3 & CAM007

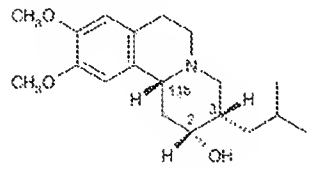
The first parts of these studies were to investigate the maximum tolerated dose of RUS 350 (Isomer B) and RUS 351 (Isomer A) (CAM003-3) and RUS 346 (Isomer D) (CAM007) in mice.

Isomer A has the following structure:



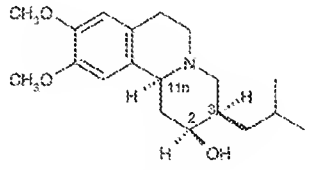
(Isomer A)

Isomer D has one of the following two structures:



2*R*,3*S*,11b*R*

OR



2*S*,3*R*,11b*S*

Doses of 3, 10, 30 & 100mg/kg were given by intra-gastric administration on days 0, 1, 2, 3 & 4. Sedation was assessed by the Catalepsy Ring Test method allowing calculation of an "immobility index" describing the % of time the animal remains motionless. At 100mg/kg RUS 350 (Isomer B) and RUS 351 (Isomer A) showed a high degree of immobility in mice after only a single administration (50-60%) and RUS 346 (Isomer D) induced total immobility 30 minutes after dosing (100%). Following

subsequent daily administration of 100mg/kg all mice in the three treatment groups showed near total or total sedation with immobility indexes of 90-100%. Repeated 30mg/kg doses caused some sedation with immobility indexes of up to 80% for RUS 346 (Isomer D), 30-40% for RUS 351 (Isomer A) and 20% for RUS 350 (Isomer B). All other doses showed negligible levels of sedation.

7. Biodynamics PF04/10

This study examined the effect of repeated dosing with RUS 351 (Isomer A) (1, 10, 20, 25 and 30mg/kg p.o.) on locomotor activity in female rats over a 10 day period. RUS 351 induced a significant reduction in locomotor activity at all doses tested but followed a dose response effect with less sedation observed at the two lowest doses (1 & 10 mg/kg) which was only significant on the last two days of testing. There was no significant effect on body weight or food and water intake at any dose suggesting that the sedation was not sufficiently severe to significantly inhibit normal feeding behaviour.

8. Biodynamics PF40/1 & PF40/2

These studies investigated the ability of tetrabenazine (TBZ), RUS 351 (Isomer A) and RUS 346 (Isomer D) to attenuate the disruption of a cognitive task induced by sub-chronic PCP treatment in rats. However, the dose of the three agents given had to be adjusted to reduce the sedating side effects measured by a reduction in locomotor activity. All three agents produced sedation at 30mg/kg p.o. A reduced dose of RUS 351 (Isomer A) at 20mg/kg produced no obvious sedation or effect on locomotor activity. The dose of RUS 346 (Isomer D) was reduced down to 10mg/kg and although at this level there was no obvious sedation visible in the animals there was a significant reduction in locomotor activity. At a concentration of TBZ of 30mg/kg, the sedation was so profound that the test dose was subsequently reduced to 5mg/kg which produced no obvious sedation or reduction in locomotor activity.

9. In summary, study AA23604 shows that tetrabenazine is more sedating than RUS 345 (Isomer C) and RUS 350 (Isomer B). The combined results of CAM003-3 and CAM007 show that RUS 351 (Isomer A) is more sedating than RUS 350 (Isomer B) and RUS

346 (Isomer D) is significantly more sedating than both RUS 351 (Isomer A) and RUS 350 (Isomer B). The combined results of PF40/1 & PF40/2 suggest that tetrabenazine is slightly more sedating than RUS 346 (Isomer D) and significantly more sedating than RUS 351 (Isomer A). In conclusion these studies suggest that the relative sedating abilities demonstrated by these compounds are in the following order TBZ > RUS 346 (Isomer D) > RUS 351(Isomer A) > RUS 345/350 (Isomers C/B). In other words, in the tests carried out in rodents, all four *cis*-dihydrotetrabenazine isomers of the '803 application were less sedating than tetrabenazine.

10. In addition to the studies carried out in rodents, Phase I clinical studies in humans have also been carried out for Isomer A (RUS351) and Isomer B (RUS350).

11. Study RD221/24655 was a randomised, double blind, placebo controlled, alternating group, ascending single dose safety, tolerability and pharmacokinetic study of Isomer A (RUS351) in healthy males given single doses up to a maximum of 100mg. No significant sedative effects were noted even at the maximum doses given.

12. Study RD 221/24249 was a randomised, double blind, placebo controlled, alternating group, ascending single dose safety, tolerability and pharmacokinetic study of Isomer B (RUS350) in healthy males given single doses up to a maximum of 100mg. Mild or moderate fatigue was noted in some subjects at higher doses (50mg and 100mg) which could reflect a mild tendency to sedation at these dose levels.

13. RD221/24250 was a randomized, double blind, placebo controlled, ascending oral multiple dose study in which healthy males were given Isomer B (RUS350) at doses of 25, 50 and 75mg once daily for seven days. There were no significant sedative effects noted at any dose level in this study.

14. In summary, there was no evidence of significant potential for sedation with Isomer A (RUS 351) up to single doses of 100mg and there was some evidence of a mild potential for sedation with Isomer B (RUS 350) at single doses of 50mg or above. This compares with tetrabenazine where sedation is the most common dose limiting

adverse event.

15. In a 12 week Phase III, randomised placebo controlled study of tetrabenazine treatment in Huntington's disease, where patients were titrated up to a maximum of 100mg tetrabenazine daily in three divided doses (maximum single dose 37.5mg), sedation/somnolence was observed in 17/54 (31%) of tetrabenazine treated patients compared with 1 (3%) of placebo treated patients and sedation was the reason that the upward titration of tetrabenazine was stopped and/or the dose of tetrabenazine was reduced in 15/54(28%) of patients (*Neurology* 2006;66:366-72, US *Xenazine* Prescribing Information).

16. In conclusion, the clinical data in man are consistent with the rat/mouse data that tetrabenazine is more sedating than the *cis*-dihydotetrabenazine isomers tested.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 100.1 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the Application or any Patent granted thereon.

P P Nichols

Philip Paul Nichols

Date 29.03.2010 (29th March 2010).